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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:

LEE

Appln. No. 08/966,223

Group Art Unit: 1645

Filed: November 7, 1997

Examiner: M.P. Allen

FOR: GDF-1

* * *

RULE 132 DECLARATION

I, Ted Ebendal, declare and state as follows:

(1) I reside at Börjegatan 45 B, S-752 29 Uppsala, Sweden.

(2) I am a Professor and Chairman in the Department of Developmental Biology, Faculty of Medicine, Uppsala University since 1988. I hold a Ph.D. (Doctor of Philosophy) degree which was earned from Uppsala University, Sweden in 1976. A copy of my *curriculum vitae* is attached.

(3) I am an author of over 100 peer-reviewed publications in the field of neuronal growth factors and neurotrophic factors.

(4) Recombinant human GDF-1 (rhGDF-1) was provided by Michael Jarpe of Cambridge NeuroScience for use in the assays reported herein.

TE

(5) On information and belief, rhGDF-1 was produced as follows. The cDNA of human GDF-1 (amino acid residues 255 to 373) was cloned into pRSET (Invitrogen). The construct was designed to produce a fusion protein which adds 34 amino acid residues to the N-terminus of rhDGF-1 including six histidine residues. There is an enterokinase cleavage site between the N-terminal extension and the rhGDF-1 sequence to facilitate removal of the tag. However, this extension was not removed for the assays reported herein.

(6) On information and belief, the above-described expression construct was inserted into the *E. coli* cell line BL21(DE3)pLysS to induce rhGDF-1 expression. Expression was induced by the addition of IPTG and was allowed to proceed for 4 hours. rhGDF-1 was produced in inclusion bodies.

(7) On information and belief, the inclusion bodies containing rhGDF-1 were solubilized and folded in 6 M guanidine and 100 mM dithiothreitol. Reducing agent and denaturing agent was removed by reverse phase HPLC. The protein was dried down in a Speed Vac and resuspended in 8 M urea at 5 mg/ml protein concentration. The protein solution was then diluted 1/100 to a final concentration of 50 µg/ml in refolding buffer of 10 mM reduced glutathione, 1 mM oxidized glutathione, and 50 mM Tris buffer (pH 9.0). The rhGDF-1 protein was allowed to refold for 20 hours at 25°C.

(8) On information and belief, a sample of the refolded rhGDF-1 protein was then analyzed by reducing and non-reducing SDS-PAGE. The gel was stained with Coomassie and the proportion of dimer was determined by densitometry. The rhGDF-1 dimer was found to be approximately 20% of total protein. The rhGDF-1 preparation was stored at -80°C.

(9) The following assays were performed under my direction and the results were analyzed by me.

(10) The sample was assayed in a fibre outgrowth assay using sympathetic ganglia from embryonic day 9 chicken embryo explanted into a collagen gel. See Ebendal et al., Journal of Neuroscience Research, vol. 40, pp. 276-284 for a description of the use of explanted ganglia in collagen gels. Neurotrophin-3 (NT-3) only weakly stimulates sympathetic fibre outgrowth in this assay (see panel d of Fig. 4 in Ernfors et al., Proceedings of the National Academy of Science, U.S.A., vol. 87, pp. 5454-5458). Members of the TGF-beta superfamily of proteins potentiate the effects of NT-3 in this assay.

(11) The sample of GDF-1 was diluted 100-fold and then further diluted in culture medium with 1% fetal calf serum as a carrier. GDF-1 was assayed on sympathetic ganglia at a

concentration of 2.5 to 250 ng/ml. The ganglia were examined after two days of incubation using darkfield microscopy. No fibre outgrowth was evoked by GDF-1 at any of these concentrations.

(12) Therefore, the potentiating effect of GDF-1 on neurotrophin activity could be assessed by comparing fibre outgrowth induced by NT-3 in the presence or the absence of GDF-1. Any increased fibre outgrowth caused by the combination of NT-3 and GDF-1 would be due to potentiation, instead of the effects of GDF-1 alone.

(13) The potentiating effect of GDF-1 in the sympathetic fibre outgrowth assay (Ernfors et al., *id.*) was determined with human NT-3 (Austral Biologicals) at a concentration of 2 ng/ml and GDF-1 at concentrations between 0 to 250 ng/ml. Fibre outgrowth density was scored in a blinded fashion by two independent observers with culture dishes arranged in random order. Scores were recorded on a scale from 0 (no fibres) to 5 (very high density of fibres forming a circular halo around the explanted nervous tissue). The assay was repeated three times. The results below represent the mean of the scores given for each culture by each observer.

| | GDF-1 concentration | Mean Score |
|---------------|---------------------|------------|
|) Medium Only | 0 ng/ml | 0.0 |
| NT-3 alone | 0 ng/ml | 1.7 |
| GDF-1 alone | 250 ng/ml | 0.0 |
| NT-3 + GDF-1 | 250 ng/ml | 3.1 |
| NT-3 + GDF-1 | 50 ng/ml | 2.3 |
| NT-3 + GDF-1 | 5 ng/ml | 1.8 |

(14) The combination of GDF-1 at 250 ng/ml with NT-3 shows a significant potentiation effect in comparison to the response obtained with NT-3 alone (statistically significant difference at $P < 0.001$ using Mann-Whitney U test). There is also a clear trend of potentiation of NT-3 by GDF-1 at 50 ng/ml, although this difference is not statistically significant in the present format of the assay.

(15) The specific activity of GDF-1 in the assay shows a reasonable dose-response relationship between 50 to 250 ng/ml.

(16) In view of the above results, I conclude that GDF-1 has biological activity on neurons similar to members of the TGF-beta superfamily of proteins.

(17) I declare further that all statements made herein of my own knowledge are true and that all statements made on

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information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

x Ted Ebendal
Ted Ebendal

x April 9, 1998
Date /

CURRICULUM VITAE for TED EBENDAL

Born: September 21, 1948. Stockholm, Sweden
Sex: Male
Marital status: Married, 1 child (born 1974)
Address: Börjegatan 45 B, S-752 29 UPPSALA, Sweden

Education/academic degrees:

1971 Bachelor of Science. Uppsala University, Sweden
1972 Master of Science, Uppsala University
1976 Doctor of Philosophy, Uppsala University
1977 Docent in Zoology, Uppsala University
1987 Professor, Faculty of Medicine, Uppsala University

Professional Experience:

1972-76 Teaching Instructor in Zoology, Uppsala University
1977 Assistant Professor in Zoology, Uppsala University
1977 Visiting scientist at Strangeways Research Laboratory, Cambridge, England
1977-81 Docent (Associate Professor) appointment in Zoology, Uppsala University
1981-87 Research Associate Professor in Neurobiology at the Swedish Natural Science Research Council
1988- Full Professor of Developmental Biology, Faculty of Medicine, Uppsala University

Scientific Awards: King Oscar Prize, Uppsala University (1982). Erik K. Fernström's prize to especially promising young scientists (1991).

Invited Oral Presentations have been given at about 80 international meetings.

Current research interests: Molecular and developmental neuroscience, development and repair mechanisms in the nervous system, neuronal growth factors and their receptors including NGF, NT-3, GDNF and BMPs. Homologous recombination in transgenic mice using embryonic stem cells.

Administrative and scientific duties at the Faculty of Medicine, Uppsala University
Chairman at the Dept of Developmental Biology (1988-). Member of the Medical Faculty Board (1988-93). Member of various scientific priority committees etc (1988-), Vice Chairman of Neuroscience Center at Uppsala University, (1989-1995).
Chairman Uppsala University Animal Research Board (1997-)

Pre-doctoral advisor: Supervised 11 PhD students of which 8 have finished their PhD thesis and three are on the way.

Post-doctoral advisor for: Wilma Friedman (USA, 1986-88), Reg Williams (Australia, 1991-94).

Organization of scientific meetings, courses etc: Organized EMBO and BMC Summer School courses for graduate students in Uppsala and at the Karolinska Institute and participated in the organization committees for international meetings in Sweden and abroad (ISDN Biennial Meeting in Tampere 1996, 5th NGF Meeting 1998).

Referee assignments etc: Exp. Cell Res., Exp. Brain Res.

Associate editor: J. Neurosci. Res., Int. J. Dev. Neurosci, Neuron, Alzheimer's Disease.

Reviewer of applications for grants and research positions: Uppsala University, Karolinska Institute, Stockholm University, Umeå University. MRC Sweden, NSF USA and various Swedish Universities.

Member of scientific committees: The Swedish Foundation for Brain Research (1995-), The International Human Frontier Science Program (Brain Functions 1996-), The Royal Swedish Academy of Sciences National Committee on Biology (1997-).

Major funding (Principal Investigator): Swedish NFR (SEK 900,000/yr for 1997 to 1999).

Publications: Over 300 scientific papers, reviews and reports in the area of developmental neuroscience

SELECTED LIST OF PAPERS PUBLISHED BY TED EBENDAL

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- Ericsson, A. 1988. Structure and expression of β -nerve growth factor in the rat central nervous system. In: Neural Development and Regeneration (ed. A. Gorio et al.). NATO ASI Series, Vol. H 22: 245-256. Springer, Berlin.
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